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Increased size and vascularisation, plus decreased echogenicity, of foetal thyroid in two-dimensional ultrasonography caused by maternal Graves' disease

Zwiększone rozmiary i unaczynienie, zmniejszona echogeniczność tarczycy płodu w ultrasonografii dwuwymiarowej spowodowane chorobą Gravesa i Basedowa u matki

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Abstract

Foetal ultrasonography monitoring is a valuable tool in assessing foetal thyroid function when pregnancy is complicated by maternal Graves' disease with accompanying high levels of TSH receptor antibodies, or when antithyroid drug therapy is instituted. Among several ultrasonographic signs of foetal thyroid disorder such as abnormalities in bone maturation and heart rhythm, cardiac failure, hydrops, intrauterine growth restriction and polyhydramnios, goitre is the most sensitive one. Here we report three cases of pregnant women with Graves' disease accompanied by very high serum levels of TSH receptor antibodies. In all three cases, as documented by foetal or neonatal serum TSH and thyroid hormones measurements, foetal thyroid dysfunction occurred. The only ultrasonographic sign of foetal involvement was a goitre with decreased echogenicity and increased vascularisation, central or peripheral. This is the first report demonstrating that a foetal thyroid gland when affected by transplacental passage of maternal TSH receptor stimulating antibodies can present exactly the same characteristic ultrasound pattern of Graves' disease as in adults. **(Endokrynol Pol 2014; 65 (1): 64–68)**

Key words: *foetal thyroid ultrasonography; maternal Graves' disease*

Streszczenie

U ciężarnej z chorobą Gravesa i Basedowa współczesne rekomendacje zalecają ultrasonograficzne monitorowanie płodu w przypadkach podwyższonego stężenia przeciwciał przeciwko receptorowi TSH lub leczenia tyreostatycznego. Spośród wielu objawów dysfunkcji tarczycy u płodu, które mogą być stwierdzone w ultrasonografii, takich jak: zaburzenia rytmu i niewydolność serca, obrzęk płodu, zaburzenia dojrzewania układu kostnego, zahamowanie wzrostu wewnątrzmacicznego i wielowodzie, najczulszym wskaźnikiem jest obecność wola. Prezentujemy 3 przypadki ciąży powikłanej matczyną chorobą Gravesa i Basedowa z towarzyszącymi bardzo wysokimi stężeniami przeciwciał przeciwko receptorowi TSH. We wszystkich 3 przypadkach wystąpiła płodowa dysfunkcja tarczycy, co potwierdzono badaniami hormonalnymi przeprowadzonymi u płodu lub noworodka. W każdym przypadku jedynym ultrasonograficznym objawem płodowej dysfunkcji tarczycy był charakterystyczny obraz gruczołu tarczowego, który wykazywał zwiększone rozmiary i unaczynienie oraz zmniejszoną echogeniczność. Jest to pierwsze doniesienie dokumentujące, że tarczyca płodu pod wpływem działania matczynych przeciwciał stymulujących receptor TSH wykazuje w badaniu ultrasonograficznym takie same charakterystyczne zmiany jak tarczyca dorosłego z chorobą Gravesa i Basedowa. **(Endokrynol Pol 2014; 65 (1): 64–68)**

Słowa kluczowe: *ultrasonografia tarczycy płodu; matczyna choroba Gravesa i Basedowa*

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Introduction

Foetal ultrasonography (US) is recommended in pregnant women with elevated TSH receptor antibodies (TRAb) or treated with antithyroid drugs (ATD) in an attempt to recognise foetal thyroid dysfunction [1–5]. The US signs of foetal thyroid dysfunction include goitre, abnormalities of bone maturation and heart rate, cardiac failure, hydrops, intrauterine growth restriction and polyhydramnios. We report three cases of pregnant women with Graves' disease in whom foetal thyroid US revealed striking abnormalities indicating foetal involvement, while other signs of foetal thyroid dysfunction were absent.

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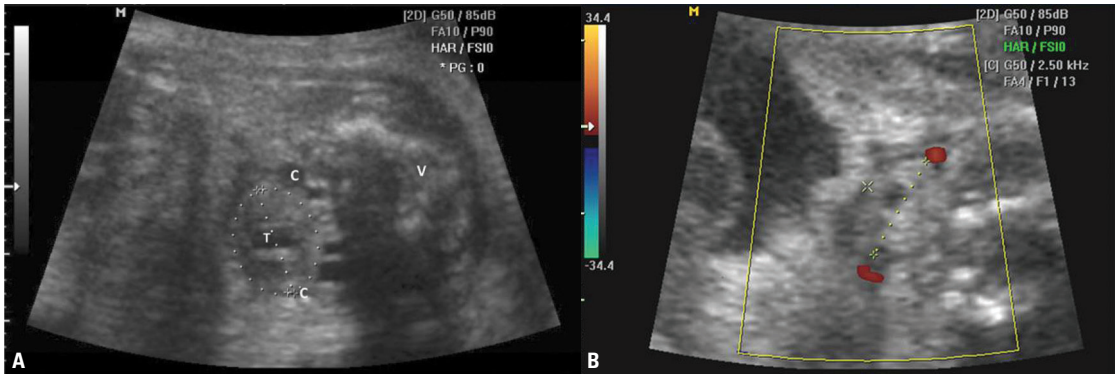

Figure 1. *Normal foetal thyroid at 31-wk gestation on US transverse scan. Thyroid gland is placed inside the calipers, with the carotid arteries outside, trachea in the middle, and cervical vertebra located posterior (***A***). Blood flow visible only within carotid arteries, absent in thyroid gland on colour Doppler examination (***B***). The examination was performed with Accuvix XQ Medison scanner and abdominal convex transducer 3–7 MHz*

Rycina 1. *Prawidłowy obraz tarczycy płodu w 31 tygodniu ciąży, przekrój poprzeczny. Gruczoł tarczowy znajduje się wewnątrz wskaźników, tętnice szyjne usytułowane są na jego obwodzie, tchawica pośrodku, krąg szyjny ku tyłowi (***A***). W badaniu kolorowego Dopplera przepływ krwi widoczny jest wyłącznie w tętnicach szyjnych, nieobecny w obrębie gruczołu tarczowego (***B***). Badanie przeprowadzono aparatem Accuvix XQ Medison z użyciem głowicy brzusznej typu convex o częstotliwości 3–7 MHz*

Case report 1

A 32-year-old woman at 37-wk gestation (WG) with an 11-year history of hypothyroidism after subtotal thyroidectomy because of Graves' hyperthyroidism was referred to the Obstetrics and Gynaecology Department. After surgery till 35 WG, she was treated with l-thyroxine (L-T4) and then L-T4 was withdrawn because of TSH suppression. Two weeks after L-T4 was stopped, the patient's results were indicative for mild hyperthyroidism: TSH 0.002 mIU/mL (normal 0.35–4.94 mIU/mL), fT4 15.55 pmol/L (normal 9.0–19.0 pmol/L), fT3 4.73 pg/mL (normal 1.71–3.71 pg/mL), TRAb > 40 IU/mL (positive results > 1.8 IUm/L). Foetal US revealed enlarged hypoechoic thyroid gland with increased central blood flow (Fig. 2). Foetal hyperthyroidism was recognised and methimazole (MMI) 10 mg daily was instituted to the mother. Normal delivery occurred at 39 WG and newborn hyperthyroidism was observed. The results obtained on the 3rd day of life were: TSH 0.001 mIU/mL (normal 1.79–9.69 mIU/mL), fT4 — 77.2 pmol/L (normal 22.5–39.9 pmol/L), fT3 — 12.7 pg/mL (normal 1.8–7.6 pg/mL), TRAb — 31.6 IU/mL.

Case report 2

A 29-year-old woman at 35 WG with hyperthyroidism diagnosed at I trimester and treated with ATD was admitted to the Obstetrics and Gynaecology Department. At 33 WG while taking MMI 5 mg daily, her TSH was 0.01 mIU/mL (normal 0.35–4.94 mIU/mL), fT4 — 9.2 pmol/L (normal 9.0–19.0 pmol/L), fT3 — 1.8 pg/mL (normal 1.71–3.71 pg/mL), TRAb — 28.6 IU/mL (positive results > 1.8 IU/mL) and foetal US revealed a goitre. Foetal hypothyroidism was suspected, and MMI was withdrawn. Two weeks later, the patient's results showed recurrence of hyperthyroidism and TRAb augmentation: TSH — 0.01 mIU/mL, fT4 — 24.6 pmol/L, fT3 — 13.4 pg/mL, TRAb > 40 IU/mL. Foetal US demonstrated hypoechoic goitre with increased central blood flow (Fig. 3). Foetal umbilical blood sampling was performed and hormonal results were mildly thyrotoxic: TSH — 0.79 mIU/mL (normal mean ± SD 6.4 ± 4.85 mIU/mL), fT4 — 25.9 pmol/L (normal mean ± SD 17.6 ± 3.0 pmol/L), fT3 — 2.45 pg/mL (normal 0.3–1.9), TRAb — 31.6 IU/mL [6, 7]. MMI 10 mg daily was instituted to the mother and one week later at 36 WG preterm delivery occurred. Mild hypothyroidism in the newborn was recognised: on the 1st day of life TSH was 31.7 mIU/mL (normal 1.79–9.69 mIU/mL), on the 2nd day TSH was 6.25 mIU/mL (normal 1.790–9.69 mIU/mL), fT4 — 11.9 pmol/L (normal 22.5–39.9 pmol/L), fT3 — 2.9 pg/mL (normal 1.8–7.6 pg/mL), and two weeks later hyperthyroidism relapsed.

Case report 3

A 33-year-old woman at 30 WG with a three-month history of hyperthyroidism treated with propylothiouracil (PTU) 150 mg daily was observed. Patient TSH was 0.033 mIU/mL (normal 0.4–4.0 mIU/mL), fT4 — 9.4 pmol/L (normal 11.5–22.7 pmol/L), fT3 — 3.97 pg/mL (normal 1.8–4.2 pg/mL), TRAb — 20.98 IU/mL (positive results > 1.8 IU/mL). Foetal US presented hypoechoic goitre with increased peripheral vascularisation (Fig. 4). Foetal hormones concentrations obtained through cordocentesis were indicative for mild hypothyroidism: TSH — 18.5 mIU/mL (normal mean ± SD 7.0 ± 3.73 mIU/mL), fT_4 — 11.0 pmol/L (normal mean ± SD 18.6

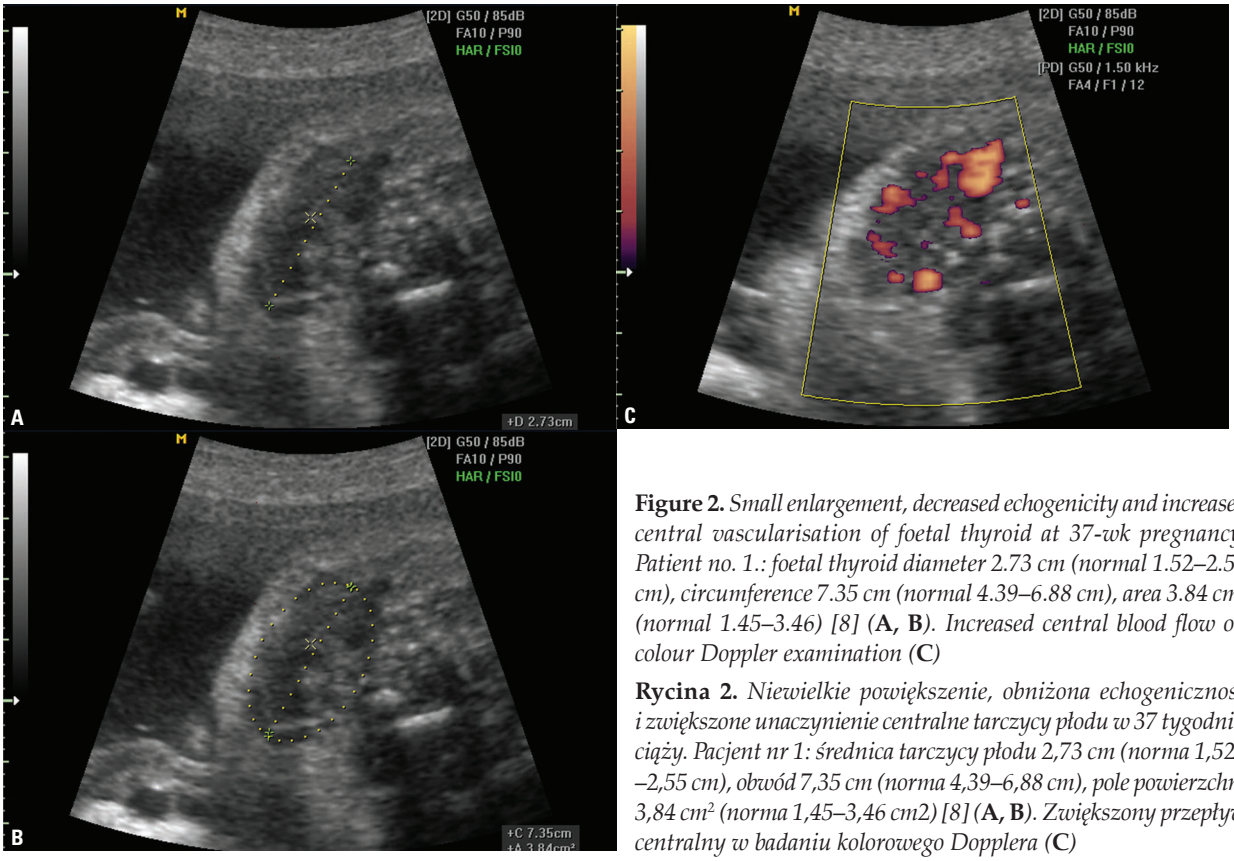

Figure 2. *Small enlargement, decreased echogenicity and increased central vascularisation of foetal thyroid at 37-wk pregnancy. Patient no. 1.: foetal thyroid diameter 2.73 cm (normal 1.52–2.55 cm), circumference 7.35 cm (normal 4.39–6.88 cm), area 3.84 cm² (normal 1.45–3.46) [8] (***A, B***). Increased central blood flow on colour Doppler examination (***C***)*

Rycina 2. *Niewielkie powiększenie, obniżona echogeniczność i zwiększone unaczynienie centralne tarczycy płodu w 37 tygodniu ciąży. Pacjent nr 1: średnica tarczycy płodu 2,73 cm (norma 1,52––2,55 cm), obwód 7,35 cm (norma 4,39–6,88 cm), pole powierzchni 3,84 cm² (norma 1,45–3,46 cm2) [8] (***A, B***). Zwiększony przepływ centralny w badaniu kolorowego Dopplera (***C***)*

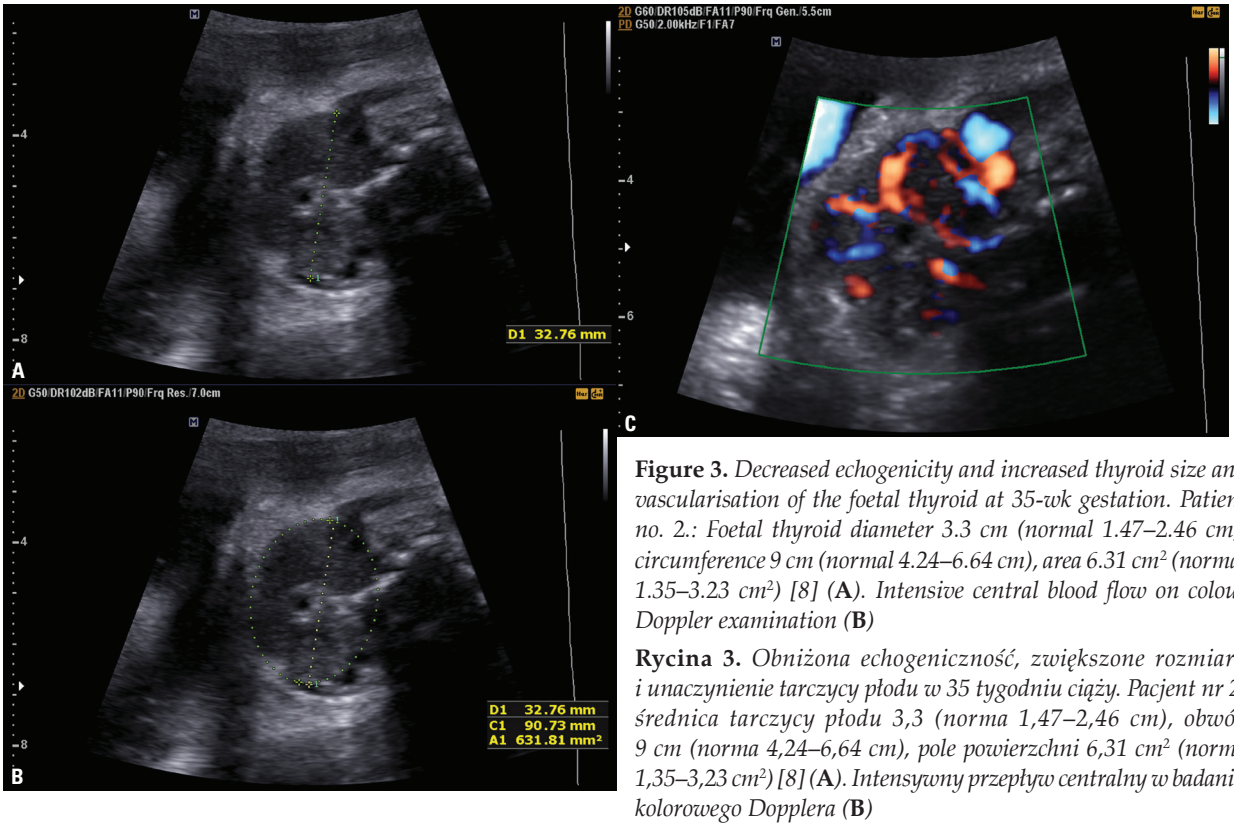

Figure 3. *Decreased echogenicity and increased thyroid size and vascularisation of the foetal thyroid at 35-wk gestation. Patient no. 2.: Foetal thyroid diameter 3.3 cm (normal 1.47–2.46 cm), circumference 9 cm (normal 4.24–6.64 cm), area 6.31 cm² (normal 1.35–3.23 cm²) [8] (***A***). Intensive central blood flow on colour Doppler examination (***B***)*

Rycina 3. *Obniżona echogeniczność, zwiększone rozmiary i unaczynienie tarczycy płodu w 35 tygodniu ciąży. Pacjent nr 2: średnica tarczycy płodu 3,3 (norma 1,47–2,46 cm), obwód 9 cm (norma 4,24–6,64 cm), pole powierzchni 6,31 cm² (norma 1,35–3,23 cm²) [8] (***A***). Intensywny przepływ centralny w badaniu kolorowego Dopplera (***B***)*

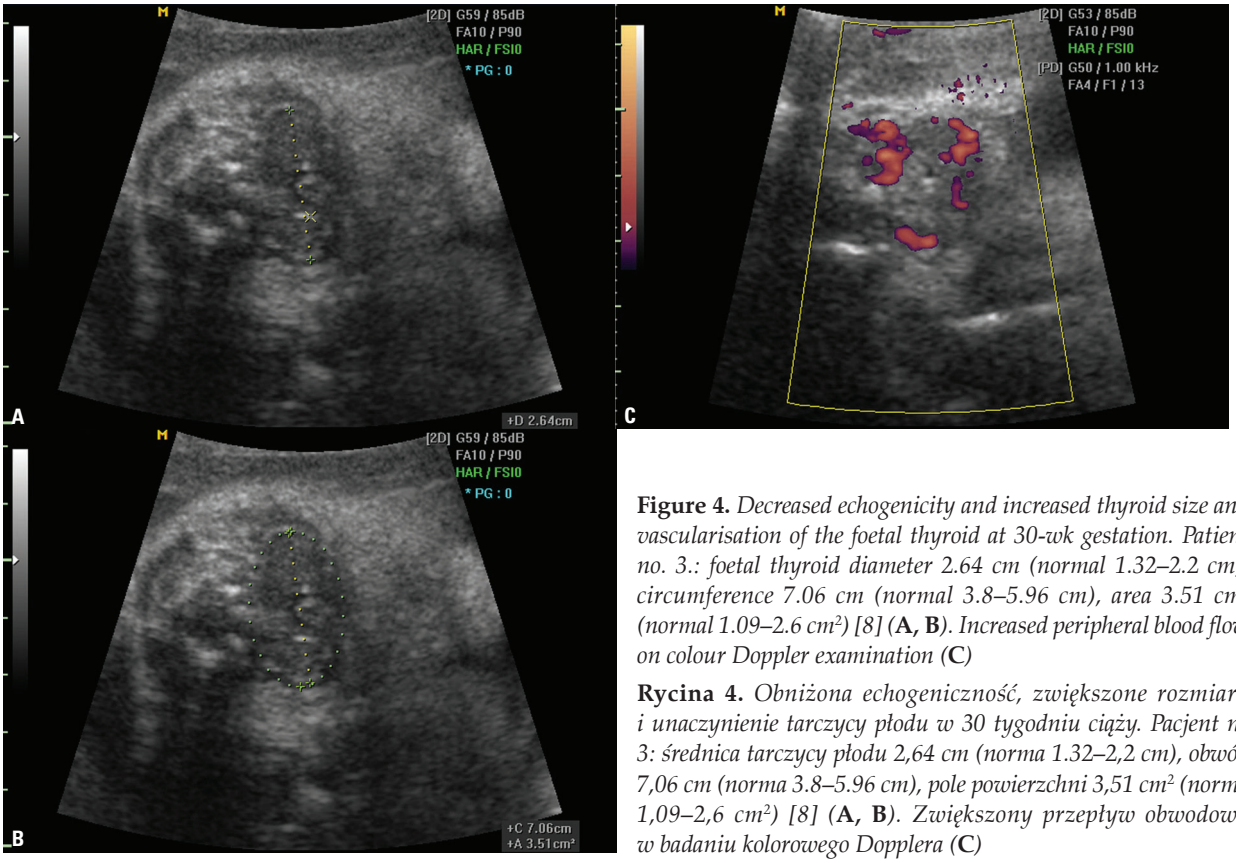

Figure 4. *Decreased echogenicity and increased thyroid size and vascularisation of the foetal thyroid at 30-wk gestation. Patient no. 3.: foetal thyroid diameter 2.64 cm (normal 1.32–2.2 cm), circumference 7.06 cm (normal 3.8–5.96 cm), area 3.51 cm² (normal 1.09–2.6 cm²) [8] (***A, B***). Increased peripheral blood flow on colour Doppler examination (***C***)*

Rycina 4. *Obniżona echogeniczność, zwiększone rozmiary i unaczynienie tarczycy płodu w 30 tygodniu ciąży. Pacjent nr 3: średnica tarczycy płodu 2,64 cm (norma 1.32–2,2 cm), obwód 7,06 cm (norma 3.8–5.96 cm), pole powierzchni 3,51 cm² (norma 1,09–2,6 cm²) [8] (***A, B***). Zwiększony przepływ obwodowy w badaniu kolorowego Dopplera (***C***)*

± 5.5 pmol/L), fT_3 — 1.17 pmol/L, TRAb — 17.28 IU/mL [6]. Maternal PTU was reduced to 25–50 mg daily and newborn TSH obtained on the 2nd day of life as a part of the neonatal screening protocol was 6.39 mIU/mL.

Discussion

To the best of our knowledge, this is the first report demonstrating that foetal thyroid gland when affected by transplacental passage of maternal TRAb can present exactly the same characteristic ultrasound pattern of Graves' disease as in adults: i.e. enlargement, hypoechogenicity and hypervascularisation. Previously, several authors reported that foetal goitre might be the first sign of foetal thyroid dysfunction: hypo- or hyper-thyroidism, when pregnancy was complicated by maternal Graves' disease [9–11]. Luton et al. observed that foetal goitre was demonstrative of foetal thyroid dysfunction with sensitivity 92%, specificity 100%, positive predictive value 100% and negative predictive value 98% [11]. Abnormalities in foetal bone maturation and foetal heart rate are both late signs of foetal thyroid dysfunction, and have been observed in 36% and 14% of affected foetuses respectively [11, 12]. There are some reports indicating that the mode of blood flow within foetal goitre enables discrimination between foetal hyperthyroidism and hypothyroidism. An increased central blood flow is most often connected with foetal hyperthyroidism caused by transplacental passage of maternal TSH receptor stimulating antibodies, while increased peripheral vascularisation might indicate foetal hypothyroidism caused by ADT overdosing [11–13].

Our observations confirm these findings and also indicate (case reports 2 and 3) that an increased blood flow is probably the very sensitive feature of foetal thyroid dysfunction as it was noted at the very early stage of foetal involvement. In two of our reported cases, cordocentesis was established; it was undertaken because of our 15 years of experience in performing this procedure and only five years' experience in assessing foetal thyroid status by US. In both patients, cordocentesis was uneventful and preterm labour, which occurred in one of them one week later, was probably caused by thyrotoxicosis.

The reported cases demonstrate how dynamic the changes in foetal thyroid status can be. Therefore very close monitoring, probably every 1–2 weeks, in foetuses at risk is needed. This is one more reason why invasive methods like cordocentesis should be limited to selected cases where clinical data is conflicting [1–5]. Although our observations confirm the very high value of foetal ultrasonography, it should be realised that the diagnosis of foetal thyroid status should consider maternal disease history, maternal serum TRAb and fT4 concentrations, and foetal US all together.

Conclusions

We have shown that a foetal thyroid gland affected by transplacental passage of maternal stimulating TRAb can demonstrate the same characteristic ultrasound features of Graves' disease as in adults: i.e. enlargement, hypoechogenicity and hypervascularisation.

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